Cancer Causes and Control **11**: 197–205, 2000.

Effects of supplemental α-tocopherol and β-carotene on colorectal cancer: results from a controlled trial (Finland)

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Received 21 December 1998; accepted in revised form 1 October 1999

Key words: α-tocopherol, β-carotene, chemoprevention, colorectal cancer, micronutrients, trial, vitamin E.

Abstract

Background: Some epidemiological investigations suggest that higher intake or biochemical status of vitamin E and β-carotene might be associated with reduced risk of colorectal cancer.
Methods: We tested the effects of α-tocopherol and β-carotene supplementation on the incidence of colorectal cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a double-blind, placebo-controlled trial among 29,133 50–69-year-old male cigarette smokers. Participants were randomly assigned to receive α-tocopherol (50 mg), β-carotene (20 mg), both agents, or a placebo daily for 5–8 years. Incident colorectal cancers (n = 135) were identified through the nationwide cancer registry, and 99% were histologically confirmed. Intervention effects were evaluated using survival analysis and proportional hazards models.
Results: Colorectal cancer incidence was somewhat lower in the α-tocopherol arm compared to the no α-tocopherol arm, but this finding was not statistically significant (relative risk (RR) = 0.78, 95% confidence interval (CI) 0.55–1.09; log-rank test $p = 0.15$). β-Carotene had no effect on colorectal cancer incidence (RR = 1.05, 95% CI 0.75–1.47; log-rank test $p = 0.78$). There was no interaction between the two substances.
Conclusion: Our study found no evidence of a beneficial or harmful effect for β-carotene in colorectal cancer in older male smokers, but does provide suggestive evidence that vitamin E supplementation may have had a modest preventive effect. The latter finding is in accord with previous research linking higher vitamin E status to reduced colorectal cancer risk.

Introduction

Colorectal cancer is the third most frequent cancer diagnosed among men and women in the US, and is similarly common in most industrialized nations, including Finland where incidence rates are, however, somewhat lower. Both heredity [1] and environmental factors – notably diet [2] – are known to influence the development of cancer of the large bowel. With respect to the latter, numerous dietary components have been studied, with available data suggesting greater risk for increased intakes of total energy, fat, and red meat, and protective associations for vegetable and fruit consumption, and for intakes of fiber, calcium, folate, vitamins D and E, and possibly carotenoids [2]. Several epidemiological investigations suggest that elevated serum concentration of α-tocopherol, the predominant form of vitamin E in humans, is associated with lower colorectal cancer risk [3]. Information regarding β-carotene is more equivocal, with greater consumption of carotenoid-rich

vegetables being more consistently related to risk reduction than intake or serology of specific carotenoids *per se* [4].

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) was a controlled supplementation trial conducted among 29,133 male smokers in Finland that tested the effectiveness of α-tocopherol and β-carotene in the primary prevention of lung cancer and other cancers [5, 6]. We report here our final findings concerning the effects of these micronutrients on the incidence of and mortality from colorectal cancer after an average of 6 years of supplementation, including exploratory analyses of possible interactions with other relevant exposures.

Materials and methods

Trial design and study population

The ATBC Study was conducted in southwestern Finland between 1985 and 1993 [5]. This primary prevention trial included 29,133 50–69-year-old male smokers (five or more cigarettes daily at entry) who were randomly assigned within each of 14 study centers to receive α-tocopherol (50 mg, as *dl*-α-tocopheryl acetate), β-carotene (20 mg), α-tocopherol and β-carotene, or placebo daily for 5–8 years (median 6.1 years) in a double-blind fashion. The 2 × 2 factorial design allowed assessment of the two intervention agents independently, with one-half of the participants receiving α-tocopherol (n = 14,564) and the other one-half not (n = 14,569); similarly, half received β-carotene (n = 14,560), and half did not (n = 14,573). Men with a prior cancer or with other serious illness, or who used vitamin E, vitamin A, or β-carotene supplements in excess of predefined doses (> 20 mg, > 20,000 IU, or > 6 mg, respectively, for the three nutrients) or anticoagulants were excluded. Written, informed consent was obtained from each participant prior to randomization. The ATBC Study was approved by the institutional review groups at both the US National Cancer Institute and the National Public Health Institute of Finland. The initial results of the ATBC Study have been previously reported [6].

Medical, dietary, smoking, and other background data were obtained at entry, along with height and weight, and a serum sample. Dietary intakes of vitamins E and C, β-carotene and other carotenoids, and alcohol were estimated from a modified diet history questionnaire [7], and were available for 27,111 participants. Serum concentrations of α-tocopherol, β-carotene, and retinol were determined by HPLC [8], and serum total cholesterol measured enzymatically. Participants had three follow-up visits annually during which information regarding illnesses and symptoms, smoking, and capsule intake were collected, and an additional serum sample was obtained after 3 years on-study. There were no losses to follow-up.

An independent Data and Safety Monitoring Board was convened twice annually to monitor trial progress and to study unblinded data relevant to intervention safety and efficacy.

Cancer case ascertainment and reviews

Colorectal cancers diagnosed through the end of the trial period, 30 April 1993, were identified through the Finnish Cancer Registry and death certificates (n = 141). Carcinoids and squamous cell cancers of the anal canal were excluded (n = 6), leaving 135 for inclusion in this report. Subsequent to our initial report of the ATBC Study findings [6], eight cases of colorectal cancer were reclassified, based on central pathology–oncology review, as not being primary malignancies of the large bowel; the revised diagnoses were three benign appendiceal carcinoids, one tubulovillous adenoma, one case each of diverticulosis and diverticulitis, and two primaries of unknown origin (one metastatic to brain and one intra-abdominal). Two separate colorectal cancers were diagnosed for each of two men during the trial; in one case the cancer diagnosed first was considered in these analyses, while in the other case the histologically confirmed cancer was used, as both tumors were diagnosed on the same date. The clinical review committee reviewed medical records to confirm and stage each case according to AJCC criteria [9]. Cases having histology available (n = 133 or 99%) were reviewed by two pathologists centrally, and classified according to the *International Classification of Diseases for Oncology* [10]. Adenocarcinoma was the histologic diagnosis in 130 of the 133 case tumors having tissue (98%). Anatomic subclassification of the cases was based on their location being proximal (*i.e.* from cecum through transverse colon) or distal (*i.e.* from splenic flexure to rectum). There was one case that was stage 0, 19 cases were diagnosed as stage I (14%), 60 (45%) as stage II, 19 (14%) as stage III, and 36 (27%) as stage IV. (Incomplete surgical dissection and examination of lymph nodes may have led to underestimation of the number of stage III cancers.) Endpoint ascertainment and review were performed blind to intervention allocation.

Sixty-nine cases continued to take study capsules post-diagnosis for a median of 13 months. These cases were proportionally distributed, as a percent of all cases, among the four intervention groups.

Deaths occuring on or before 30 April 1993 were identified through the Central Population Registry and the underlying cause of death was reviewed by a study physician. Only deaths having colorectal cancer as the underlying cause (ICD-9 153, 154.0, or 154.1) were included in the analyses of colorectal cancer mortality (n = 46).

Statistical analysis

In all trial analyses the "intention-to-treat" principle was used with all subjects being allocated to the intervention arm as randomized. Follow-up time accumulated until the date of first colorectal cancer diagnosis, the date of death, or 30 April 1993. Cases of cancer other than colorectal were ignored in the analyses. Kaplan–Meier cumulative incidence curves were plotted for the four intervention groups and for the two intervention agents separately. Two-sided nominal *p*-values were derived from the unweighted log-rank statistic [11]. The trial intervention effect was assessed using multiplicative proportional hazard regression models [11], with time since randomization modeled nonparametrically, and an indicator variable for each intervention included. The relative risks (RR) of colorectal cancer incidence and mortality and their 95% confidence intervals (CI) are reported. Interaction between the intervention effects of α-tocopherol and β-carotene was tested using a separate model with a cross-products term. Of several potential risk factors, only age, body mass index, and serum cholesterol were significantly related to colorectal cancer occurrence, but because they had no effect on the estimated intervention effects, were not included in the intervention models. Effect modification by baseline factors was assessed through subgroup (*i.e.* stratum-specific) hazard regression models for estimation of intervention relative risk, and in separate models, the relevant cross-product terms (*e.g.* intervention group × baseline factor (continuous)) provided the statistical test for interaction. Intervention group differences in case stage distributions and survival time were tested using the chi-squared and Wilcoxon rank sum tests, respectively.

The relationship between risk of colorectal cancer and serum concentrations of α-tocopherol and β-carotene achieved during supplementation in the respective intervention groups could be evaluated only among those participants for whom the 3-year follow-up serum sample had been obtained and colorectal cancer had not yet been diagnosed. These multiplicative proportional hazards models utilized tertiles of follow-up serum concentrations, and included age, body mass index, and serum cholesterol, to adjust for possible differences among the tertiles, and the other intervention (*e.g.* an indicator variable for β-carotene supplementation was included in the models of follow-up serum α-tocopherol in the α-tocopherol arm).

The association between colorectal cancer incidence and baseline dietary intakes and serum concentrations of α-tocopherol and β-carotene was estimated through proportional hazards models that included intervention group, age, body mass index, and serum cholesterol.

Results

The four trial intervention groups were well balanced for all baseline characteristics evaluated (Table 1). Several factors measured during follow-up, such as diet and alcohol intake, nonstudy vitamin supplementation, body mass index, and cigarette smoking, also remained essentially equivalent across intervention groups. Four out of five participants took over 95% of their capsules during the trial, and this high level of adherence was equal across the groups. Increases in serum α-tocopherol and β-carotene over baseline concentrations were observed in the active supplement groups after 3 years, from 11.5 to 17.3 mg/L for α-tocopherol among those receiving α-tocopherol (11.4 and 12.4, respectively, in the non-α-tocopherol arm), and from 0.17 to 3.0 mg/L for β-carotene in the β-carotene arm (0.17 and 0.18 mg/L, respectively, in those not receiving β-carotene).

There were 169,460 person-years of observation during the study, and 135 men were diagnosed with incident colorectal cancer: 29 in the α-tocopherol alone group, 30 in the α-tocopherol plus β-carotene group, 39 in the β-carotene alone group, and 37 in the placebo group. The Kaplan–Meier curves of cumulative incidence for the four groups are shown in Figure 1. From the proportional hazards model the relative risk for colorectal cancer incidence, compared to placebo, was 0.79 (95% confidence interval (CI) 0.48–1.28) for the α-tocopherol alone group, 0.82 (CI 0.50–1.32) for the α-tocopherol plus β-carotene group, and 1.06 (CI 0.68–1.66) for those receiving only β-carotene. There was no interaction between the α-tocopherol and β-carotene interventions ($p = 0.96$).

Cumulative incidence of colorectal cancer remained lower throughout most of the trial among those receiving α-tocopherol than among those not supplemented with α-tocopherol, particularly after 2 years of supplementation (Figure 2). By the end of the study colorectal cancer incidence, though not statistically significantly different, was 22% lower (RR = 0.78; CI 0.55–1.09) among those receiving α-tocopherol compared to those not. Colorectal cancer incidence did not differ between

Table 1. Baseline characteristics of participants according to intervention group, Finnish men[1]

	Intervention group			
	AT	AT + BC	BC	Placebo
Number of subjects	7286	7278	7282	7287
Age (years)	57.2	57.3	57.2	56.9
Cigarettes/day	20	20	20	20
Body mass index (kg/m^2)	26.1	26.0	25.9	26.0
Serum cholesterol (mmol/L)	6.15	6.18	6.15	6.14
Serum α-tocopherol (mg/L)	11.4	11.6	11.5	11.5
Serum β-carotene (μg/L)	168	172	170	171
Serum retinol (μg/L)	574	577	576	577
Dietary intake (daily)				
Energy (kcal)	2736	2714	2721	2710
Fat (g)	118	117	118	116
Fiber (g)	24.2	24.3	24.3	24.1
Cholesterol (mg)	540	542	540	535
Alcohol (ethanol, g)	11.3	10.8	11.0	10.8
Vitamin E (mg)	10.7	10.8	10.8	10.6
β-carotene (mg)	1.70	1.73	1.70	1.72
Vitamin C (mg)	87.5	88.5	88.3	88.1
Calcium (g)	1.35	1.34	1.34	1.33
Selenium (μg)	86.2	86.3	86.3	85.4
$\geq$ Moderate work activity (%)	26	26	25	26
$>$ Elementary school education (%)	21	22	21	21

[1] Median values or percent. AT = α-tocopherol, BC = β-carotene. Dietary intake data are per day and available for 6773, 6763, 6757, and 6817 participants in the four groups, respectively. Work activity among workers only.

the β-carotene study arm and the non-β-carotene arm (RR = 1.05; CI 0.75–1.47; Figure 3).

The modest relative incidence difference according to α-tocopherol supplementation arm was somewhat greater for cancers located proximal to the splenic flexure (15 *versus* 23 cases) compared to more distal large bowel cancers (44 *versus* 51); there was no material difference in the effect of β-carotene according to anatomic location. With respect to disease stage, there were 10, 23, 10 and 16 colorectal cancer cases diagnosed in the

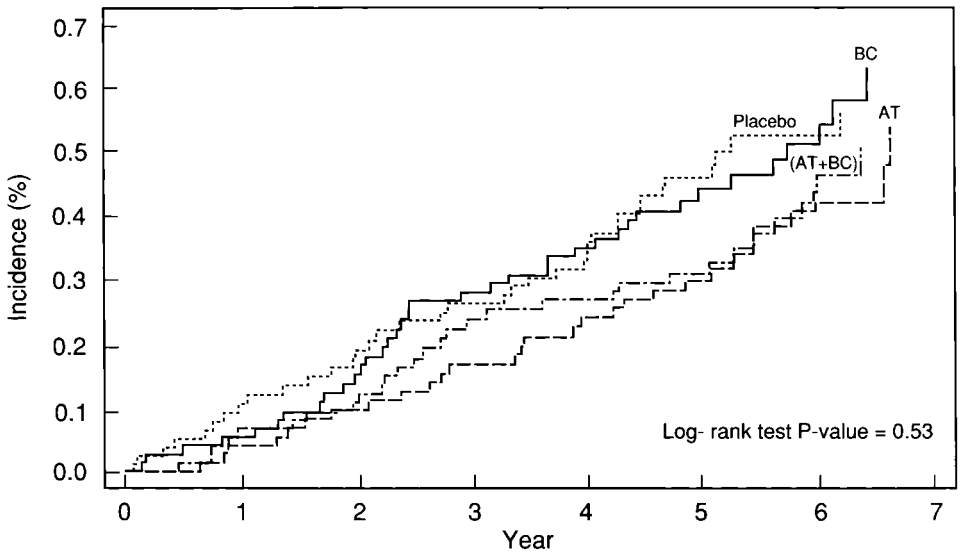

Fig. 1. Cumulative incidence of colorectal cancer according to intervention group allocation in the ATBC Cancer Prevention Study, Finland.

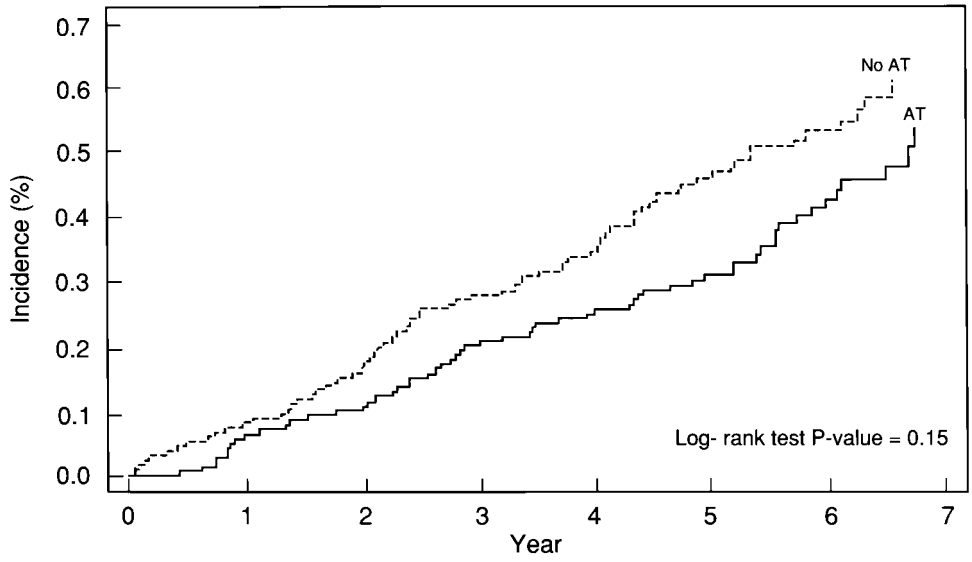

Fig. 2. Cumulative incidence of colorectal cancer according to α-tocopherol supplementation group in the ATBC Cancer Prevention Study, Finland.

α-tocopherol study arm in stages 0/I, II, III, and IV, respectively, compared to 10, 37, 9, and 20 in the non-α-tocopherol arm. Similarly, among those receiving β-carotene there were 8, 30, 12, and 19 cases diagnosed in the same stages, respectively, compared to 12, 30, 7, and 17 in the non-β-carotene arm. These intervention group distributions by subsite and stage did not differ significantly by the chi-squared test.

There were 46 deaths from colorectal cancer, 12 in the α-tocopherol only group, 13 in the β-carotene only group, 10 in the α-tocopherol plus β-carotene group, and 11 in the placebo group. Colorectal cancer mortality was similar in the α-tocopherol and non-α-tocopherol study arms (RR = 0.92; CI 0.51–1.64), as well as in the β-carotene and the non-β-carotene arms (RR = 1.01; CI 0.56–1.79). Neither supplement affected colorectal cancer survival time.

Although the main intervention effects were not statistically significant, exploratory subgroup analyses based on baseline factors potentially relevant to colo-

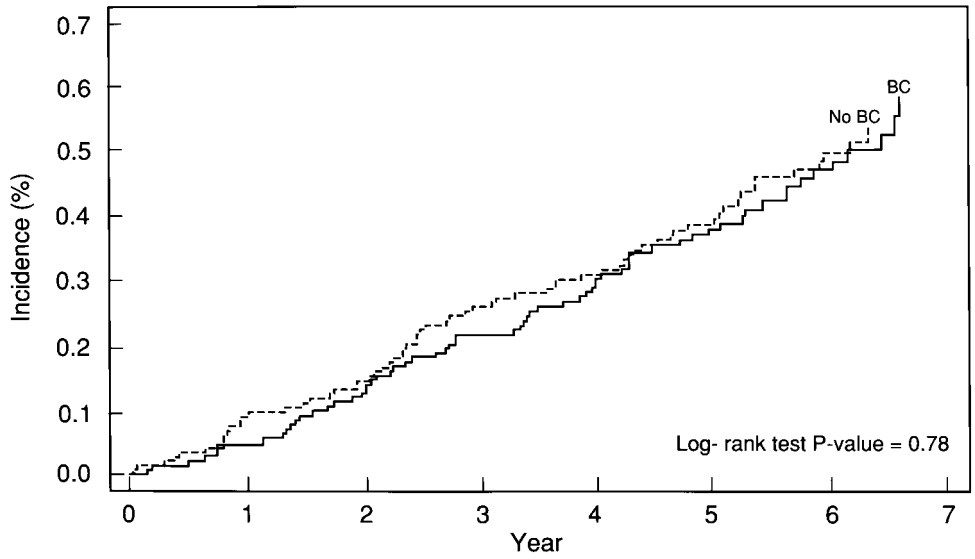

Fig. 3. Cumulative incidence of colorectal cancer according to β-carotene supplementation group in the ATBC Cancer Prevention Study, Finland.

rectal cancer or the effectiveness of the study agents were conducted. We observed little evidence suggestive of modification of the α-tocopherol and β-carotene supplementation effects (Table 2). There was a suggestion of lower incidence resulting from the α-tocopherol supplementation among men with higher baseline dietary intake of energy. There was no β-carotene–alcohol interaction, and no evidence of effect modification by other dietary nutrients including selenium, folate, vitamin C, or calcium, or by baseline vitamin E or β-carotene supplement use (data not shown). Follow-up serum α-tocopherol and β-carotene concentrations were not significantly related to colorectal cancer risk in the respective active intervention arms (data not shown).

The prevalence at baseline and during supplementation of several gastrointestinal-related symptoms that could have led to earlier diagnosis – including nausea, heartburn, intestinal cramps, diarrhea, and constipation – were equivalent among the four intervention groups.

We observed no statistically significant associations between colorectal cancer risk and baseline dietary or serum β-carotene, dietary vitamin E, or serum α-tocopherol, adjusting for baseline age, body mass index, serum cholesterol, and intervention group (data not shown).

Table 2. Relative risk (RR) of colorectal cancer for the α-tocopherol and β-carotene supplementation groups according to levels of selected baseline characteristics, Finnish men[1]

	Alpha-tocopherol *vs.* No alpha-tocopherol		Beta-carotene *vs.* No beta-carotene	
	RR	*p*-Value	RR	*p*-Value
Total	0.78		1.05	
Age (years)				
≤57	0.92	0.48	1.15	0.69
>57	0.71		0.99	
Body mass index (kg/m^2)				
≤26.0	0.80	0.86	0.85	0.27
>26.0	0.75		1.25	
Serum α-tocopherol (mg/l)				
≤11.6	0.94	0.32	1.09	0.89
>11.6	0.67		1.04	
Serum β-carotene (μg/l)				
≤170	0.80	0.89	1.11	0.73
>170	0.77		0.98	
Dietary intake (daily)				
Energy (kcal)				
≤2720	1.08	0.05	1.00	0.88
>2720	0.52		0.95	
Fat (g)				
≤117	1.05	0.08	1.29	0.15
>117	0.56		0.77	
Fiber (g)				
≤24	0.95	0.22	0.96	0.92
>24	0.61		0.99	
Vitamin E (mg)				
≤10.7	1.01	0.09	1.17	0.29
>10.7	0.55		0.80	
β-carotene (mg)				
≤1.71	0.61	0.29	0.77	0.22
>1.71	0.89		1.19	
Alcohol (ethanol, g)				
≤11	0.89	0.41	0.99	0.88
>11	0.64		0.94	

[1] Strata based on study population medians. Dietary intake data available for 27,111 participants. *p*-Value for intervention–characteristic interaction is for the (intervention arm × continuous factor) cross-product term in separate proportional hazards models.

Discussion

We observed a statistically nonsignificant, 22% reduction in the incidence of colorectal cancer in response to daily supplementation with α-tocopherol, 50 mg, for an average of 6 years. β-Carotene supplementation had no effect on large bowel cancer incidence, and neither nutrient affected colorectal cancer mortality or survival time.

Although the suggested preventive effect of α-tocopherol may be due to the relatively small number of events and therefore chance, there are several important strengths of our study to keep in mind. The large controlled trial design essentially eliminates the potential impact of confounding of vitamin supplement use by other lifestyle correlates that typically limit interpretation of observational studies. Endpoint ascertainment was complete, and histological confirmation of malignancy was made for all but two cases. The 5–8 years of supplementation with 50 mg (or IU) *dl*-α-tocopheryl acetate and 20 mg β-carotene resulted in 50% and 17-fold higher serum concentrations of these micronutrients, and corroborate the reported excellent compliance. It is possible, however, that stronger intervention effects may have been observed were higher dosages (primarily of vitamin E) or a longer study duration utilized.

Findings from prior trials of vitamin E or β-carotene for the prevention of colorectal cancer, adenomas, or polyps among high-risk subjects have not been encouraging. Regarding vitamin E, an early prevention trial tested the effects of daily supplementation with both α-tocopherol (400 mg) and vitamin C (4 g) on rectal polyps among 58 women and men with familial adeno-

matous polyposis coli who had previously undergone a colectomy [12]. Nonsignificantly lower (by 35%) prevalence of polyps was found after 4 years among those receiving the two vitamins and given a high fiber supplement. A study of 255 post-polypectomy patients conducted in Italy showed that, compared to nontreatment, daily supplementation with a combination of vitamins A (30,000 IU), C (1 g), and E (70 mg) for an average of 18 months reduced the recurrence rate of adenomatous polyps from 36% to 6% [13]. By contrast, no effect on colorectal polyp recurrence was observed for a combination of vitamin E and C (400 mg each) in a 2-year Canadian trial conducted among 143 participants [14], and a similar result was obtained for colorectal adenomas in the Polyp Prevention Study of 864 participants using vitamins E (400 mg) and C (1 g) daily for 4 years (RR = 1.08; CI 0.91–1.29) [15]. The possible reduction in cancer of the large bowel we observed in response to supplementation with 50 mg α-tocopherol in this large, population-based trial is therefore singular, and will require confirmation in other controlled studies.

Observational studies do, however, provide some support for a beneficial relationship between serum α-tocopherol, or dietary or supplemental vitamin E intake, and colorectal cancer. Five prospective studies examined serum α-tocopherol status and found lower serum levels among those who subsequently developed colorectal cancer [16–20]. A pooled analysis revealed an adjusted estimate of 30% lower risk for the highest as compared to the lowest quartile of serum α-tocopherol concentration [3]. One follow-up study of dietary vitamin E intake reported no association with the incidence of colon or colorectal cancer [21], and an earlier report from the same cohort suggested a nonsignificant inverse relationship (RR = 0.8; CI 0.4–1.5) [22]. Another cohort study, conducted among women in Iowa and involving 212 colorectal cancers, showed a substantial 50% reduction in colon cancer incidence for vitamin E supplement use, and an estimated relative risk of 0.32 for the highest *versus* lowest quintile of vitamin E intake from diet plus supplements [23]. Case–control studies have also reported significant inverse associations for higher dietary vitamin E intake [24], or for supplemental vitamin E use of ≥200 IU daily (*versus* none; RR = 0.43; CI 0.26–0.71) [25]. Other investigations reveal no substantive relationship between dietary vitamin E and colorectal cancer [26–28], and in the present study there was no overall association for serum α-tocopherol or dietary vitamin E intake at baseline.

Laboratory experiments demonstrate vitamin E-related reductions in cell culture malignant tranformations [29] and in dimethylhydrazine-induced colon tumor incidence in mice [30] and rats [31], though not consistently [32]. There are several plausible mechanisms through which α-tocopherol, the most biologically active form of vitamin E, could influence the development of colorectal cancer. It has a strong inherent potential for antioxidation of highly reactive and genotoxic electrophyles, such as hydroxyl, superoxide, lipid peroxyl and hydroperoxyl, and nitrogen radicals [33], which could prevent propagation of free radical damage in biological membranes, and decrease mutagenesis and carcinogenesis. α-Tocopherol also inhibits protein kinase-C activity [34, 35], and the proliferation of smooth muscle cells [34, 36], melanoma cells [37], and rectal mucosa [38], though one experiment showed no antiproliferative effect in the colon [39]. Such antiproliferative activity may be relevant to the suggested enhanced α-tocopherol effect we observed among participants having higher daily energy (and possibly higher fat) intake [40]. Vitamin E also induces the detoxification enzyme NADPH : quinone reductase in colon cancer cell lines [41], and inhibits arachadonic acid metabolism [42]. Diminished fecal mutagenicity in response to vitamin E supplementation has also been reported [43].

Our findings for β-carotene are consistent with results reported from two other large intervention trials that tested β-carotene supplementation among average-risk subjects and showed no efficacy for colorectal cancer prevention. The Physicians' Health Study involved 22,071 male physicians in the US and reported 167 cases of large-bowel cancer in its β-carotene group (50 mg on alternate days) and 174 cases in the placebo group after 12 years of supplementation [44]. Similarly, the Beta-Carotene and Retinol Efficacy Trial (CARET) studied 18,314 men and women in the US at elevated risk for lung cancer and tested daily supplementation with β-carotene (30 mg) in combination with retinyl palmitate (25,000 IU) for an average of 4 years [45]; no difference in colorectal cancer incidence was observed between the active treatment and placebo arm (RR = 1.02; CI 0.70–1.50). The Polyp Prevention Study [15] also reported no effect of β-carotene 25 mg daily on colorectal adenoma recurrence, compared to placebo (RR = 1.01; CI 0.85–1.20), while the Australian Polyp Prevention Project suggested greater adenoma recurrence in its β-carotene group (RR = 1.5; CI 0.9–2.5) [46]. The combined trial data therefore make it unlikely that pharmacologic doses of supplemental β-carotene are beneficial in the prevention of colorectal cancer. By contrast, observational epidemiologic studies suggest an inverse association between dietary β-carotene (or other carotenoids) and risk of colorectal cancer, although not consistently, and with the evidence being both more abundant and more convincing for high vegetable (or vegetable and fruit) consumption *per se* [2, 4, 47].

Although prevention of colorectal cancer by vitamin E was not the primary hypothesis in the ATBC Study, the present secondary findings suggest that such benefit may have been observed. These results are made more plausible by currently available, supportive laboratory and human observational data, and to some degree by our recent report of prostate cancer prevention [48], which showed significant efficacy from vitamin E for the first time from a large controlled trial. β-Carotene had no apparent preventive effect in colorectal cancer, bringing to three the number of large-scale trials having such an outcome. Other large-scale trials of vitamin E can help to define the true role of this vitamin in colorectal cancer prevention.

Acknowledgements

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) was supported by Public Health Service contract NO1-CN-45165 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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